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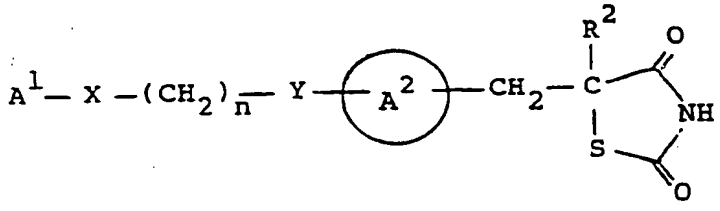
(54) **Thiazolidine dione derivatives.**

(57) A compound of formula (I) :



(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:
A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;
A^2 represents a benzene ring having in total up to five substituents;
X represents O, S or NR^1 wherein R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl

EP 0 419 035 A1

group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
Y represents O or S;
R^2 represents an alkyl, aralkyl or aryl group; and
n represents an integer in the range of from 2 to 6; a process for the preparation of such a compound, a pharmaceutical composition comprising such compound and the use of such compound and composition in medicine.

NOVEL COMPOUNDS

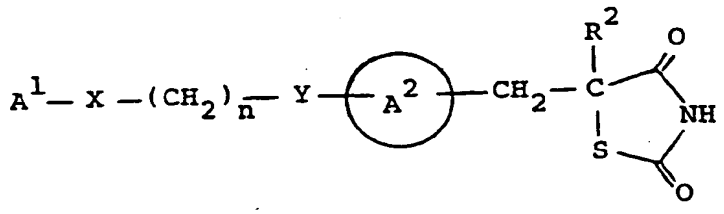
This invention relates to certain substituted thiazolidinedione derivatives, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

European Patent Applications, Publication Numbers 0008203, 0139421, 0155845, 0177353, 0193256, 0207581, 0208420 and 0306228 relate to thiazolidinedione derivatives which are disclosed as having hypoglycaemic and hypolipidaemic activity. Chem. Pharm. Bull 30 (10) 3580-3600 also relates to certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activities.

It has now surprisingly been discovered that certain novel substituted-thiazolidinedione derivatives show improved blood-glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and are of particular use in the treatment of Type II diabetes.

These compounds are also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

Accordingly, the present invention provides a compound of formula (I):



(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

A^2 represents a benzene ring having in total up to five substituents;

X represents O, S or NR^1 wherein R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

Y represents O or S;

R^2 represents an alkyl, aralkyl or aryl group; and

n represents an integer in the range of from 2 to 6.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

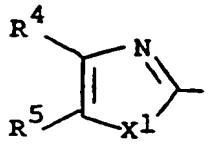
Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

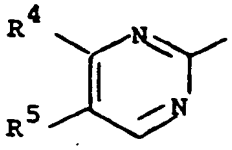
Suitable values for A^1 when it represents a 5- membered aromatic heterocyclyl group include thiazolyl and oxazolyl, especially oxazolyl.

Suitable values for A^1 when it represents a 6- membered aromatic heterocyclyl group include pyridyl or pyrimidinyl.

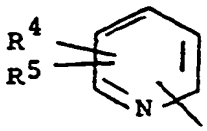
Suitably R^2 represents an alkyl group, in particular a C_{1-6} alkyl group, for example a methyl group. Preferably, A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

wherein:

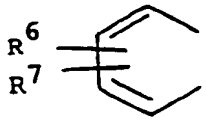
R^4 and R^5 each independently represents a hydrogen atom, an alkyl group or a substituted or unsubstituted aryl group or when R^4 and R^5 are each attached to adjacent carbon atoms, then R^4 and R^5 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^4 and R^5 together may be substituted or unsubstituted; and in the moiety of formula (a), X^1 represents oxygen or sulphur.

Aptly, A^1 represents a moiety of the abovedefined formula (a).

Aptly, A^1 represents a moiety of the abovedefined formula (b).

Aptly, A^1 represents a moiety of the abovedefined formula (c).

In one favoured aspect R^4 and R^5 together represent a moiety of formula (d):



(d)

wherein R^6 and R^7 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^6 and R^7 each independently represent hydrogen, halogen, alkyl or alkoxy.

Favourably, R^6 represents hydrogen. Favourably, R^7 represents hydrogen.

Preferably, R^6 and R^7 both represent hydrogen.

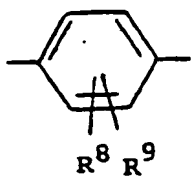
In a further favoured aspect R^4 and R^5 each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group and more favourably, R^4 and R^5 each independently represent hydrogen, alkyl or phenyl.

Preferably, for the moiety of formula (a), R^4 and R^5 together represent the moiety of formula (d).

Preferably, for the moieties of formula (b) or (c), especially (c), R^4 and R^5 both represent hydrogen.

Suitable substituents for the moiety A^2 include halogen, substituted or unsubstituted alkyl or alkoxy.

Favourably, A^2 represents a moiety of formula (e):



(e)

wherein R^8 and R^9 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^8 and R^9 each independently represent hydrogen, halogen, alkyl or alkoxy.

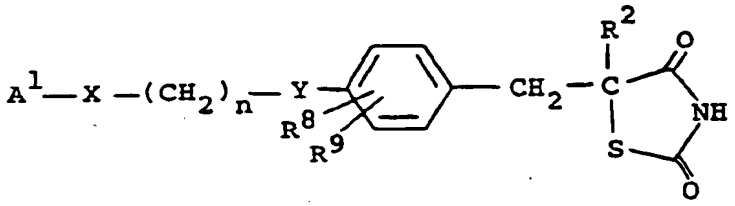
Preferably, R^8 and R^9 each represent hydrogen.

Favourably, X represents oxygen. Favourably, X represents sulphur. Preferably, X represents the above defined moiety NR^1.

Favourably, Y represents O. Favourably Y represents S.

In one preferred aspect the present invention provides a class of compounds, which fall wholly within

the scope of formula (I), of formula (II):



(II)

or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein A^1, X, Y, R^2 and n are as defined in relation to formula (I) and R^8 and R^9 are as defined in relation to formula (e).

Suitably, n represents an integer 2, 3 or 4, notably 2 or 3 and especially 2.

Suitably in the moiety NR^1, R^1 represents hydrogen, alkyl, acyl, especially acetyl, or benzyl.

Preferably in the moiety NR^1, R^1 represents a methyl group.

As indicated above a compound of formula (I) may exist in one of several tautomeric forms, all of which are encompassed by the present invention. It will be appreciated that the present invention encompasses all of the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

When used herein the terms 'alkyl' and 'alkoxy' relate to groups having straight or branched carbon chains,containing up to 12 carbon atoms.

Suitable alkyl groups are C_{1-12} alkyl groups, especially C_{1-6} alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

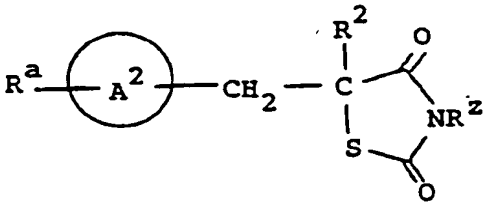
Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable acyl groups include alkylcarbonyl groups, especially C_{1-6} alkylcarbonyl groups, for example acetyl groups.

Suitable pharmaceutically acceptable salts include salts of the thiazolidinedione moiety, and, where appropriate, salts of carboxy groups.

Suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxyalkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tris-(2-hydroxyethyl)amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

In a further aspect the present invention also provides a process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable hydrate thereof, which process comprises reacting a compound of formula (III):



(III)

wherein R^2 and A^2 are as defined in relation to formula (I), R^z is hydrogen or a nitrogen protecting group and R^a is a moiety convertible to a moiety of formula (f):

A^1-X-$(CH_2)_n$-Y- (f)

wherein A^1, X, Y and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a into the said moiety (f) and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any protecting group;

(iii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

Suitably, R^a represents HX-$(CH_2)_n$-Y- wherein X, Y and n are as defined in relation to formula (I), although Y is preferably -O-.

When R^a is HX-$(CH_2)_n$-Y-, an appropriate reagent capable of converting R^a into a moiety (f) is a compound of formula (IV):

A^1 - R^x (IV)

wherein A^1 is as defined in relation to formula (I) and R^x represents a leaving group.

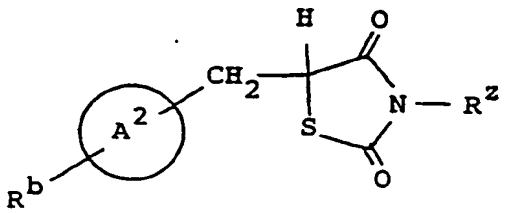
A suitable leaving group R^x includes a halogen atom, preferably a chlorine or bromine atom, or a thioalkyl group for example a thiomethyl group.

Suitable values of HX-$(CH_2)_n$-Y- include HO$(CH_2)_n$-O-.

The reaction between the compound of formula (III) and the appropriate reagent may be carried out under conditions suitable to the particular compound of formula (III) and the reagent chosen; thus for example the abovementioned reaction between a compound of formula (III) wherein R^a represents HX-$(CH_2)_n$-Y- and the compound of formula (IV), may be carried out in any suitable solvent, for example dimethylformamide, at a temperature which provides a suitable rate of formation of the compound of formula (I), for example at an elevated temperature in the range of from 50°C to 120°C, preferably in the presence of a base such as sodium hydride.

Alternatively, in the reaction between a compound of formula (IV) and a compound of formula (III) wherein R^a represents HX-$(CH_2)_n$-Y- and wherein X is NR^1, the reaction may conveniently be carried out in a solvent such as chloroform at a low to medium temperature, for example in the range of from 0° to 30°C, preferably in the presence of a base such as triethylamine.

A compound of formula (III) may be prepared by reacting a compound of formula (V):



(V)

wherein A^2 is as defined in relation to formula (I), R^z is as defined in relation to formula (III) and R^b is a moiety R^a or a moiety convertible into a moiety R^a, with a compound of formula (VI):

R^2 - R^c (VI)

wherein R^2 is as defined in relation to formula (I) and R^c represents a leaving group, such as a halogen atom, for example an iodine atom; and thereafter, if required, converting a moiety R^b into a moiety R^a.

Preferably, R^2 in formula (VI) represents alkyl or aralkyl.

The reaction between a compound of formula (V) and (VI) may be carried out in any suitable solvent

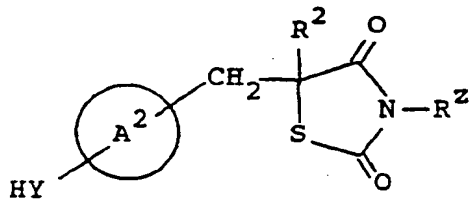
such as 1,2-dimethoxyethane, at any temperature providing a convenient rate of formation of the required product, suitably at ambient temperature, and preferably in the presence of a base such as an alkali metal base, for example potassium amide in liquid ammonia.

A suitable value for R^b is $-YR^d$ wherein Y is as defined in relation to formula (I) and R^d is a hydrogen atom or, more suitably in the reaction between compounds of formula (V) and (VI), a protecting group such as a benzyl group.

Any conversion of R^b into R^a may involve a number of steps and thus when R^d represents a protecting group the conversion would comprise an appropriate deprotection step, for example a debenzylation step, using standard methods of deprotection, for example debenzylation may be effected by hydrogenolysis.

When R^a represents $HX-(CH_2)_n-Y-$, a suitable value for R^b is -YH, wherein Y in R^b and in the resulting R^a have the same value.

The moiety R^b may be converted into the moiety R^a by any suitable means, for example when R^b represents -OH or -SH and R^a represents $HX-(CH_2)^n-O-$ or $HX-(CH_2)_n-S-$the appropriate conversion may be carried out by coupling a compound of formula (VA):



(VA)

wherein R^2, Y and A^2 are as defined in relation to formula (I) and R^z is as defined in relation to formula (III) with a compound of formula (VII):

$R^e-X-(CH_2)_n-OR^f$ (VII)

wherein X and n are as defined in relation to formula (I), Re is a protecting group and, when Y in the compound of formula (VA) represents -O-, R^f is hydrogen or, when Y in compound (VA) represents -S-, then R^f is a tosylate or mesylate group; and thereafter, if required removing any protecting group.

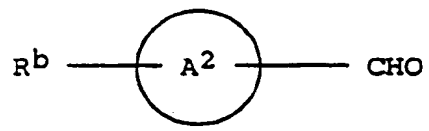
When Y in (VA) is -O- and R^f in (VII) is hydrogen, the reaction is generally carried out in the presence of a suitable coupling agent, a suitable coupling agent being provided by diethyl azodicarboxylate and triphenylphosphine. The coupling reaction may be carried out in any suitable solvent at a low to medium temperature, for example in tetrahydrofuran at a temperature in the range of between 0 and 60 °C.

When Y in (VA) is -S- and R^f in (VII) represents tosylate or mesylate, the reaction between (VA) and (VII) is suitably carried out in an aprotic solvent, such as dimethylformamide, at a low to elevated temperature, for example in the range of from 50 °C to 120 °C and preferably in the presence of a base such as sodium hydride.

A compound of formula (VII) wherein R^f represents a tosylate or a mesylate group may conveniently be prepared from a compound of formula (VII), wherein R^f represents hydrogen, using conventional tosylation or mesylation methods.

A suitable protecting group R^e is a benzyl group.

A compound of formula (V) may be prepared by reacting a compound of formula (VIII):



(VIII)

wherein A^2 is as defined in relation to the compound of formula (I) and R^b is as defined in relation to formula (V), with 2,4-thiazolidinedione and reducing the product so formed; and thereafter if necessary converting a moiety R^b into a moiety R^a.

The reaction between the compound of formula (VIII) and 2,4-thiazolidinedione will of course be carried out under conditions suitable to the nature of the compound of formula (VIII), in general the reaction being

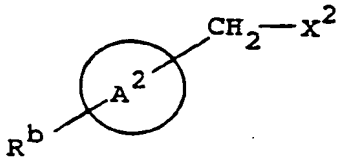
carried out in a solvent such as toluene, suitably at an elevated temperature such as the reflux temperature of the solvent and preferably in the presence of a suitable catalyst such as piperidinium acetate or benzoate. Favourably, in the reaction between the compound of formula (VIII) and 2,4-thiazolidinedione, the water produced in the reaction is removed from the reaction mixture, for example by means of a Dean and Stark apparatus.

A suitable reduction method for the abovementioned reduction includes catalytic reduction or the use of a metal/solvent reducing system.

Suitable catalysts for use in the catalytic reduction are palladium on carbon catalysts, preferably a 10% palladium on charcoal catalyst; the reduction being carried out in a solvent, for example dioxan, suitably at ambient temperature.

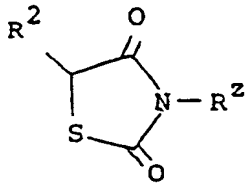
Suitable metal/solvent reducing systems include magnesium in methanol.

A compound of formula (III) may also be prepared by reacting a compound of formula (IX):



(IX)

wherein A^2 and R^b are as defined in relation to formula (V) and X^2 is a halogen atom, with a compound of formula (X):



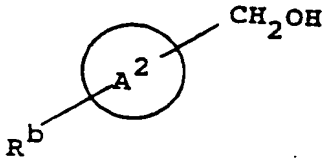
(X)

wherein R^2 is as defined in relation to formula (I) and R^z is as defined in relation to formula (III); and thereafter if required, converting a moiety R^b into a moiety R^a.

The reaction between the compounds of formula (IX) and (X) may be carried out in any suitable solvent, suitably 1,2-dimethoxyethane, at any temperature providing a convenient rate of formation of the required product, suitably at ambient temperature and preferably in the presence of a base such as an alkali metal base, for example potassium amide in liquid ammonia.

Suitably, X^2 represents a chlorine atom.

A compound of formula (IX) may be prepared from a compound of formula (XI):



(XI)

wherein A^2 and R^b are as defined in relation to formula (V), by reaction of the compound of formula (XI) with a halogenating reagent.

Suitable halogenating agents are conventional halogenating agents, for example when X^2 represents a chlorine atom, a suitable halogenating agent is thionyl chloride.

The conditions for the reaction between the compound of formula (XI) and the halogenating agent will of course depend largely upon the nature of the particular halogenating agent chosen, but the conditions are

generally the conventional conditions appropriate to the particular halogenating agent used, for example suitable conditions when the halogenating agent is thionyl chloride involve the use of methylene chloride or chloroform as solvent at a low to medium temperature for example a reaction temperature of between 0 and 30°C.

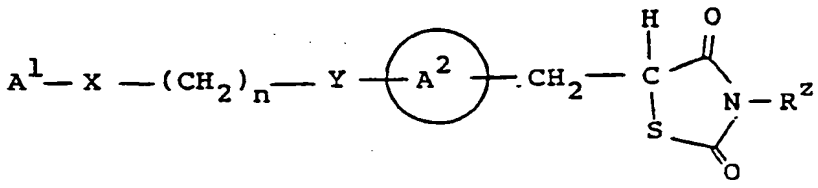
The compounds of formula (IV), (VI), (VII), (VIII) and (XI) are generally known commercially available compounds or are prepared using methods analogous to those used to prepare such compounds.

The compounds of formula (X) are known compounds or they are prepared according to procedures used to prepare known compounds, for example compounds of formula (X) are disclosed in DE 3045059.

Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art for example those disclosed in 'Protective Groups in Organic Synthesis', Wiley Interscience, 1981, T.W. Greene. Thus, for example, a suitable nitrogen protecting group is a benzyl group or a benzyloxycarbonyl group and a suitable hydroxyl or thiol protecting group is a benzyl group or a p-methoxybenzyl group.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected and includes those methods disclosed in the abovementioned 'Protective Groups in Organic Synthesis'.

A compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be prepared by reacting a compound of formula (XII):



(XII)

wherein A^1, A^2, X and Y are as defined in relation to formula (I) and R^z is as defined in relation to formula (III), with a compound of the hereinbefore defined formula (VI); and thereafter if required carrying out one or more of the following optional steps:

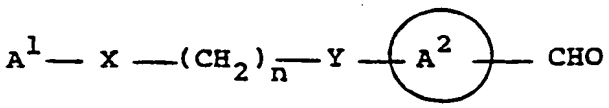
(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any protecting group;

(iii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

The reaction between the compounds of formulae (XII) and (VI) may conveniently be carried out under analogous conditions to those described above for the reaction between compounds of formulae (V) and (VI).

A compound of formula (XII) may suitably be prepared by reacting a compound of formula (XIII):



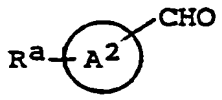
(XIII)

wherein A^1, A^2, X, Y and n are as defined in respect of the compound of formula (I), with 2,4-thiazolidinedione and thereafter reducing the product so formed.

The reaction between a compound of formula (XIII) and 2,4-thiazolidinedione may suitably be carried out under analogous conditions to those used in the reaction between a compound of formula (VIII) and 1 2,4-thiazolidinedione.

Suitable reduction methods include those disclosed above for preparing the compounds of formula (V).

A compound of formula (XIII) may be prepared by reacting a compound of formula (XIV):



(XIV)

wherein A^2 is as defined in relation to formula (I) and R^a is as defined in relation to formula (III), with an appropriate reagent capable of converting R^a to a moiety of the above defined formula (f).

Suitable values for R^a include $HX-(CH_2)_n-Y-$ wherein X, Y and n are as defined in relation to the compound of formula (I). When R^a represents $HX-(CH_2)_n-Y-$ the appropriate compound of formula (XIV) may be reacted with a reagent of the abovedefined formula (IV) to provide the required compound of formula (XII).

Suitable reaction conditions for the reaction of the compound of formula (XIV) and the appropriate reagent may include those described above in relation to the preparation of compound (III) with the said appropriate reagent.

Favourably, in the compound of formula (XIV), R^a represents a leaving group, especially a fluorine atom. When Ra represents a leaving group, preferably a fluorine atom, a particularly appropriate reagent is a compound of formula (XV):

$A^1-X-(CH_2)_n-YH$ (XV)

wherein A^1, X, Y and n are as defined in relation to formula (I).

The reaction between the compounds of formulae (XIV) and (XV) may be carried out under any suitable conditions, for example in a solvent such as dimethylformamide or dimethylsulphoxide at an elevated temperature for example in the range of between 100 to 150° C, suitably in the presence of a base such as sodium hydride or potassium carbonate.

Suitably, in the compound of formula (XIV), R^a represents a hydroxyl group or a thiol group, and a particularly appropriate reagent is a compound of the abovedefined formula (XV) or a compound of formula (XVA):

$A^1-X-(CH_2)_n-OR^q$ (XVA)

wherein A^1, X and n are as defined in relation to formula (XV) and R^q represents a tosylate or mesylate group.

The reaction between the compound of formula (XIV) wherein R^a is a hydroxyl group and the reagent of the above defined formula (XV) may suitably be carried out in an aprotic solvent, such as tetrahydrofuran, at low to medium temperature, for example at ambient temperature, and preferably in the presence of a coupling agent such as that provided by triphenylphosphine and diethyl azodicarboxylate.

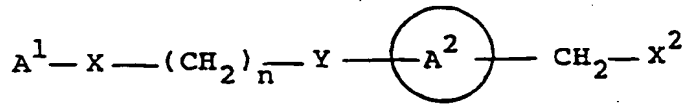
The reaction between the compound of formula (XIV), wherein R^a is a hydroxyl group or a thiol group, and the reagent of the abovedefined formula (XVA) may be carried out in an aprotic solvent, such as dimethylformamide, at a low to elevated temperature, for example in the range of from 50° C to 120° C and preferably in the presence of a base, such as sodium hydride.

The compound of formula (XVA) may be prepared from the corresponding compound of formula (XV) by reaction with either a tosyl halide or a mesyl halide in a solvent such as pyridine.

The compounds of formula (XIV) are known compounds or they are compounds prepared by methods analogous to those used to prepare known compounds, for example 4-fluorobenzaldehyde and 4-hydroxybenzaldehyde are known commercially available compounds and 4-mercaptobenzaldehyde may be prepared as outlined in Beilstein 8.I.533.

A compound of formula (XII) may also be prepared according to the procedures described in EP0306228.

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be prepared by reacting a compound of formula



(XVI)

wherein A^1, A^2, X, Y and n are as defined in relation to formula (I) and X^2 represents a halogen atom, with a compound of the hereinbefore defined formula (X); and thereafter if required carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

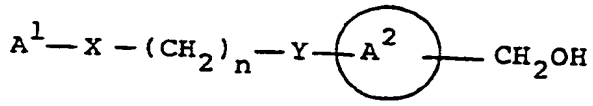
(ii) removing any protecting group;

(iii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

Suitably X^2 in the compound of formula (XVI) represents a halogen atom, favourably a chlorine atom.

The reaction between the compounds of formulae (X) and (XVI) may suitably be carried out under analogous conditions to those described above for the reaction between the compounds of formulae (IX) and (X).

A compound of formula (XVI) may be prepared by reacting a compound of formula (XVII):



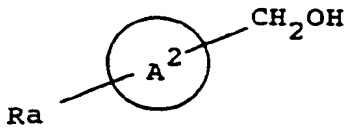
(XVII)

wherein A^1, A^2, X, Y and n are as defined in relation to formula (I), with a halogenating agent.

Suitable halogenating agents are conventional halogenating agents, for example when X^2 represents a chlorine atom, a suitable halogenating agent is thionyl chloride.

The conditions for the reaction between the compound of formula (XVII) and the halogenating agent will of course depend largely upon the nature of the particular halogenating agent chosen, but the conditions are generally the conventional conditions appropriate to the particular halogenating agent used, for example suitable conditions when the halogenating agent is thionyl chloride involve the use of methylene chloride or chloroform as solvent at a low to medium temperature for example a reaction temperature of between 0 and 30°C.

A compound of formula (XVII) may be prepared by reacting a compound of formula (XVIII):



(XVIII)

wherein A^2 and R^a are as defined in relation to formula (III), with an appropriate reagent capable of converting a moiety R^a into a moiety of the above defined formula (I).

The nature of the moiety R^a, the nature of the appropriate reagent and suitable reaction conditions for the reaction between the compound of formula (XVIII) and the appropriate reagent are as described above for the reaction between a compound of formula (III) and the appropriate reagent.

Where necessary a compound of formula (XVIII) may be prepared from a compound of the abovedefined formula (XI), by converting a moiety R^b into a moiety R^a, using methods hereinbefore described.

The abovementioned conversion of a compound of formula (I) into a further compound of formula (I) includes converting one group R^1 into another group R^1.

The conversion of a compound of formula (I) into a further compound of formula (I) may be carried out by using any appropriate conventional procedure. Thus, suitable conversions of one group R^1 into another group R^1 includes converting a group R^1 which represents hydrogen into a group R^1 which represents an acyl group.

The conversion of a compound of formula (I) wherein R^1 represents hydrogen into a compound of formula (I) wherein R^1 represents acyl may be carried out using any appropriate conventional acylation procedure, such as by treating an appropriately protected compound of formula (I) with an acylating agent. For example acetic anhydride may be used to prepare the compound of formula (I) wherein R^1 is acetyl.

It will be appreciated that in the abovementioned conversion any reactive group in the compound of formula (I) would be protected, according to conventional chemical practice, where necessary.

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically

acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

The compounds of formula (III), (V), (IX), (XII), (XVI) and (XVII) are believed to be novel compounds and as such form a further aspect of the invention.

The compounds of formula (XVIII) are known commercially available compounds or they may be prepared according to methods analogous to those used to prepare known compounds.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties: the present invention accordingly provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

In a further aspect the present invention also provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

As indicated hereinbefore the present invention also provides a compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a human or non-human mammal in need thereof.

The present invention further provides a method for the treatment of hyperlipidaemia in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of hyperglycaemia in humans, and/or the treatment and/or prophylaxis of hyperlipidaemia human, the compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In the treatment and/or prophylaxis of hyperglycaemia in non-human mammals, especially dogs, the active ingredient may be adminstered by mouth, usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemia in non-human mammals.

The dosages regimens for the treatment of hypertension, cardiovascular disease and eating disorders will generally be those mentioned above in relation to hyperglycaemia.

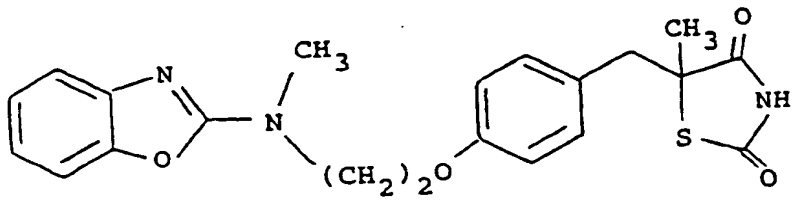
In a further aspect the present invention provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

The present invention also provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders.

The following Procedures and Examples illustrate the invention but do not limit it in any way.

Example 1

5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxyl benzyl)-5-methyl-2,4-thiazolidinedione.

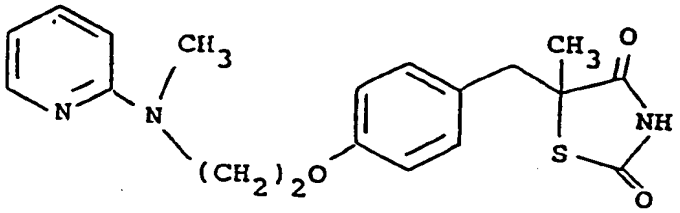


To a stirred solution of potassium amide, prepared from potassium metal (0.69g) in liquid ammonia (150ml), was added a solution of 5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione (2.35g, prepared according to procedures described in EP 0306228) in dry 1,2-dimethoxyethane (30ml). The resulting suspension was allowed to stir for 30 minutes. A solution of methyl iodide (2.52g) in dry 1,2-dimethoxyethane (30ml) was added rapidly and the reaction mixture left to stir for one hour, before being neutralized with solid ammonium chloride (2g). The mixture was left open to air and stirred for a further hour, acidified (2M HCl) and left stirring overnight. The mixture was added to water (100 ml), neutralized (2.5M NaOH; sodium bicarbonate solution) and extracted with ethyl acetate (3x150ml). The combined organic extracts were washed with sodium metabisulphite solution (200 ml), brine (200ml), dried ($MgSO_4$), filtered and evaporated to dryness. The title compound (mp 66-70° C) was obtained as a foam following chromatography on silica-gel of the residual oil in 1% methanol in dichloromethane.

^1H NMR δ ($CDCl_3$) : 1.75 (3H,s); 2.95 (1H,d); 3.25 (1H,d); 3.3 (3H,s); 3.9 (2H,complex); 4.2 (2H,complex); 6.8 (2H,d); 6.95-7.35 (6H,complex); 9.25 (1H,broad s exchanges with D_2O)

Example 2

5-(4-[N-Methyl-N-(2-pvridyl)amino)ethoxylbenzyl)-5-methyl-2,4-thiazolidinedione



The title compound was obtained as a foam from 5-(4-[N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazol idinedione and iodomethane in an analogous procedure to that used in Example 1.
^{1}H NMR ($CDCl_3$:
1.75 (3H,s); 3.15 (3H,s); 2.9-3.8 (2H, complex); 3.6-4.2 (6H, complex); 6.5 (2H, complex); 6.75 (2H, d); 7.10 (2H, d); 7.45 (1H, complex); 8.10 (1H, d); 9.5-12.5 (1H, v. broad s, exchanges with D_2O).

DEMONSTRATION OF EFFICACY OF COMPOUNDS

Obese Mice, Oral Glucose Tolerance Test.

C57bl/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powdered oxoid diet containing the test compound. After 8 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3 g/kg). Blood samples for glucose analysis were taken 0, 45, 90 and 135 minutes after glucose administration and the results appear below as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control groups. 7 mice were used for each treatment.

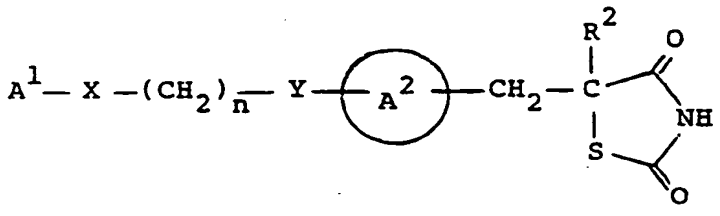
EXAMPLE NO:	LEVEL IN DIET (μmol kg^{-1} of DIET)	%REDUCTION IN AREA UNDER BLOOD GLUCOSE CURVE
1	300	40
2	300	22

Toxicology

No toxicological effects were indicated for any of the compounds of the invention in any of the abovementioned tests.

Claims

1. A compound of formula (I):



(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, characterised in that:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

A^2 represents a benzene ring having in total up to five substituents;

X represents O, S or NR^1 wherein R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

Y represents O or S;

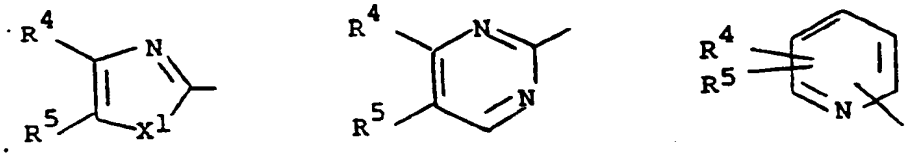
R^2 represents an alkyl, aralkyl or aryl group; and

n represents an integer in the range of from 2 to 6.

2. A compound according to claim 1, wherein R^2 represents an alkyl group.

3. A compound according to claim 1 or claim 2, wherein R^2 represents a methyl group.

4. A compound according to any one of claims 1 to 3, wherein A^1 represents a moiety of formula (a), (b) or (c):

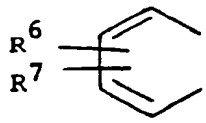


(a) (b) (c)

wherein:

R^4 and R^5 each independently represents a hydrogen atom, an alkyl group or a substituted or unsubstituted aryl group or when R^4 and R^5 are each attached to adjacent carbon atoms, then R^4 and R^5 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^4 and R^5 together may be substituted or unsubstituted; and in the moiety of formula (a), X^1 represents oxygen or sulphur.

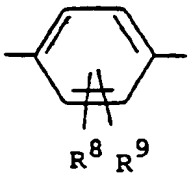
5. A compound according to claim 4, wherein R^4 and R^5 together represent a moiety of formula (d):



(d)

wherein R^6 and R^7 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

6. A compound according to any one of claims 1 to 5, wherein A^2 represents a moiety of formula (e):



(e)

wherein R^8 and R^9 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

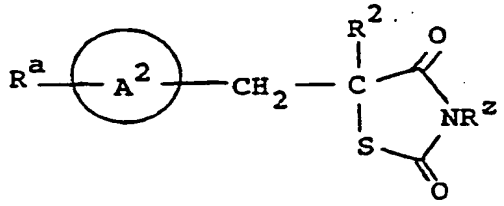
7. A compound according to any one of claims 1 to 6, wherein Y represents O.

8. A compound according to claim 1, being 5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy] benzyl)-5-methyl-2,4-thiazolidinedione;

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof.

9. A process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable hydrate thereof, characterised in that the process comprises:

i) reacting a compound of formula (III):



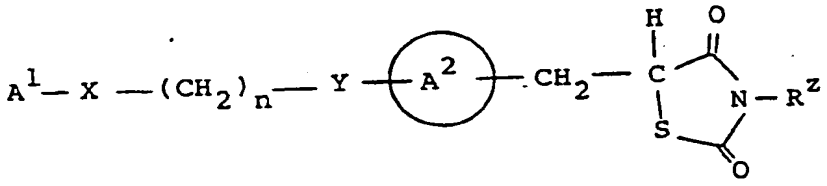
(III)

wherein R^2 and A^2 are as defined in relation to formula (I) in claim, 1 R^z is hydrogen or a nitrogen protecting group and Ra is a moiety convertible to a moiety of formula (f):

A^1-X-$(CH_2)_n$-Y- (f)

wherein A^1, X, Y and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a into the said moiety (f);

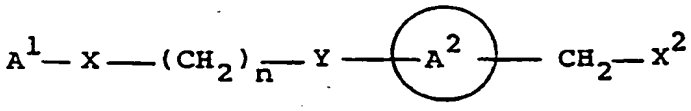
ii) by reacting a compound of formula (XII):



(XII)

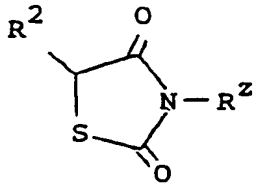
wherein A^1, A^2, X and Y are as defined in relation to formula (I) in claim 1 and R^z is as defined in relation to formula (III), with a compound of the hereinbefore formula (VI) as defined in reaction I) above; or

iii) by reacting a compound of formula (XVI):



(XVI)

wherein A^1, A^2, X, Y and n are as defined in relation to formula (I) in claim 1 and X^2 represents a halogen atom, with a compound of formula (X);



(X)

wherein R^2 is as defined in relation to formula (I) in claim 1 and R^2 is as defined in relation to formula (III) in reaction I) above; and thereafter if required carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any protecting group;

(iii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

10. A pharmaceutical composition comprising a compound of formula (I) according to claim 1, or a tautomeric form thereof or a pharmaceutically acceptable salt thereof or pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

11. A compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

12. A compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

13. A compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia and/or hypertension and/or cardiovascular disease and/or certain eating disorders.

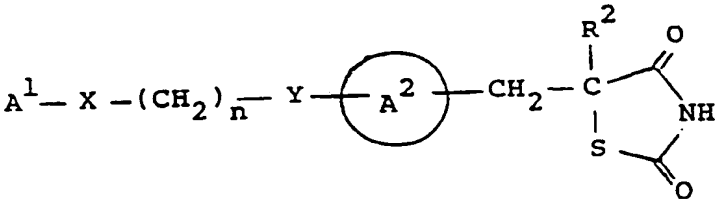
14. The use of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

15. The use of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia and/or hypertension and/or cardiovascular disease and/or certain eating disorders.

Claims for the following Contracting State: ES

1. A process for preparing a compound of formula

(I):



(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

A^2 represents a benzene ring having in total up to five substituents;

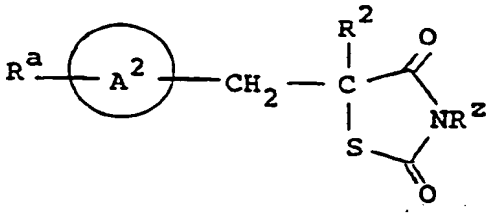
X represents O, S or NR^1 wherein R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

Y represents O or S;

R^2 represents an alkyl, aralkyl or aryl group; and

n represents an integer in the range of from 2 to 6, characterised in that the process comprises:

i) reacting a compound of formula (III):



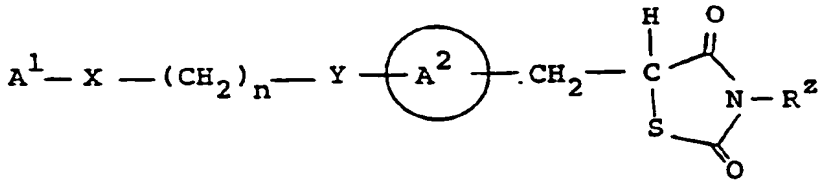
(III)

wherein R^2 and A^2 are as defined in relation to formula (I) in claim, 1 R^z is hydrogen or a nitrogen protecting group and Ra is a moiety convertible to a moiety of formula (f):

A^1-X-$(CH_2)_n$-Y- (f)

wherein A^1, X, Y and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a into the said moiety (f);

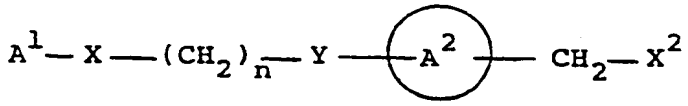
ii) by reacting a compound of formula (XII):



(XII)

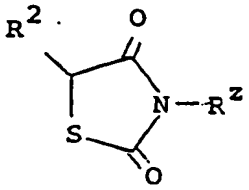
wherein A^1, A^2, X and Y are as defined in relation to formula (I) in claim 1 and R^z is as defined in relation to formula (III), with a compound of the hereinbefore formula (VI) as defined in reaction i) above; or

iii) by reacting a compound of formula (XVI):



(XVI)

wherein A^1, A^2, X, Y and n are as defined in relation to formula (I) in claim 1 and X^2 represents a halogen atom, with a compound of formula (X);



(X)

wherein R^2 is as defined in relation to formula (I) in claim 1 and R^z is as defined in relation to formula (III) in reaction i) above; and thereafter if required carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

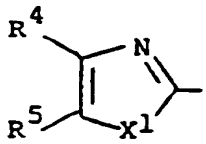
(ii) removing any protecting group;

(iii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

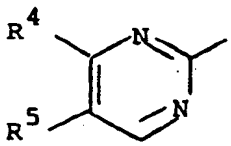
2. A process according to claim 1, for preparing a compound wherein R^2 represents an alkyl group.

3. A process according to claim 1 or claim 2, for preparing a compound wherein R^2 represents a methyl group.

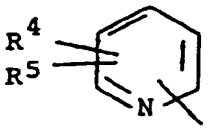
4. A process according to any one of claims 1 to 3, for preparing a compound wherein A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)

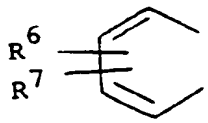


(c)

wherein:

R^4 and R^5 each independently represents a hydrogen atom, an alkyl group or a substituted or unsubstituted aryl group or when R^4 and R^5 are each attached to adjacent carbon atoms, then R^4 and R^5 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^4 and R^5 together may be substituted or unsubstituted; and in the moiety of formula (a), X^1 represents oxygen or sulphur.

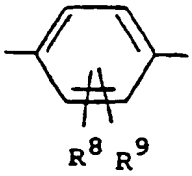
5. A process according to claim 4, for preparing a compound wherein R^4 and R^5 together represent a moiety of formula (d):



(d)

wherein R^6 and R^7 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

6. A process according to any one of claims 1 to 5, for preparing a compound wherein A^2 represents a moiety of formula (e) :



(e)

wherein R^8 and R^9 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

7. A process according to any one of claims 1 to 6, for preparing a compoundwherein Y represents O.

8. A process according to claim 1, for preparing 5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy] benzyl)-5-methyl-2,4-thiazolidinedione;

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof.

9. The use of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

10. The use of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 30 9027

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,D	EP-A-306228 (BEECHAM GROUP PLC) * pages 2 - 4, line 49 *	1, 10	C07D277/34 C07D417/12 A61K31/425 //(C07D417/12, 277:00,213:00) (C07D417/12, 277:00,239:00) (C07D417/12, 277:00,263:00) (C07D417/12, 277:00,277:00)
A	EP-A-257781 (TAKEDA CHEMICAL INDUSTRIES,LTD.) * pages 3 - 4 *	1, 10	
A,D	EP-A-208420 (TAKEDA CHEMICAL INDUSTRIES,LTD) * pages 1 - 3, line 11 *	1, 10	
P,A	WO-A-8908652 (PFIZER INC.) 21 September 1989 * pages 7 - 9, line 2 *	1, 10	
P,X	EP-A-356214 (BEECHAM GROUP PLC) 28 February 1990 * the whole document *	1, 10	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D277/00
C07D417/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	05 DECEMBER 1990	KYRIAKAKOU, G.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
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2